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NARRATIVE REVIEW

The medical management of acute respiratory distress syndrome

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Abstract

Despite advancements in bedside monitoring and paradigm shifts in standard ventilatory practice, mortality from acute respiratory distress syndrome (ARDS) remains high. The recent Global ARDS definition adopts a more pragmatic approach enabling earlier identification across a broader patient spectrum, independent of the interventions being administered. Meanwhile, our understanding of managing this heterogeneous syndrome has shifted towards defining precise subgroups with shared therapeutic targets. Physiological, biological, and radiological phenotypes may modify the response to interventions previously showing indeterminate benefit, making them potentially central to future personalised ARDS management. This narrative review summarises core evidence for the medical and ventilatory management of ARDS, explores emerging concepts, and offers clinicians a framework for current best practice and a roadmap for possible future directions.

Keywords: Mechanical ventilation, Ventilator-induced lung injury, Positive end-expiratory pressure, Acute hypoxemic respiratory failure

Background

There have been four major attempts to define acute respiratory distress syndrome (ARDS) since Ashbaugh and colleagues' seminal case series in 1967 [1]. The evolving nature of global health underscores the need to re-examine syndromic entities such as ARDS in terms of pathophysiology, phenotyping, and management in the context of both traditional and emerging causes. In this regard, while the global ARDS definition has moved a step towards clinical pragmatism and away from treatment-dependent dichotomies, it implies that the identification of ARDS is going to be more frequent and earlier than in previous decades [2]. Broadening the inclusion criteria of an already heterogeneous syndrome further strengthens the case for the need to tailor management based on specific treatment-responsive subgroups.

Structured clinical guidelines for the management of ARDS have also been recently updated and published [3, 4]. This review aims not to appraise the definition, but rather expand on core and emerging evidence to provide clinicians with a framework on which to refine and personalise the delivery of accepted, but broad management principles. Disease-specific diagnostic and treatment strategies and the use of extracorporeal life support are beyond the scope of this review.

Determinants of ARDS phenotypes and disease severity

ARDS is a heterogeneous syndrome, and many trials have identified heterogeneity of treatment response. Grouping patients according to radiological, physiological, or biological phenotypes may assist in targeting interventions

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to patients with the highest probability of benefit (so-called predictive enrichment).

Oxygenation

Classification of ARDS severity assessed by the degree of hypoxaemia measured through partial pressure of oxygen (PaO_2) or oxygen saturation (SpO_2) relative to the inspired fraction of oxygen (FiO_2) correlates with outcome. Hospital mortality in patients with mild ($200 < PaO_2/FiO_2 \leq 300$ mmHg or $235 < SpO_2/FiO_2 \leq 315$), moderate ($100 < PaO_2/FiO_2 \leq 200$ mmHg, or $148 < SpO_2/FiO_2 \leq 235$), and severe ($PaO_2/FiO_2 \leq 100$ mmHg, or $SpO_2/FiO_2 \leq 148$) ARDS is globally estimated at 35%, 40%, and 46%, respectively, with some geographical variation [5, 6]. However, there are issues with using the PaO_2/FiO_2 or SpO_2/FiO_2 ratio, including the dependence on positive end-expiratory pressure (PEEP), FiO_2, volume history (impact of recent recruitment or ventilation strategies on end-expiratory lung volume), and other factors. For these reasons, some trials have specified that classification occurs after optimisation of appropriate ventilatory support prior to enrolment [7, 8].

Importantly, the improvement in outcomes associated with a number of interventions, including low tidal volume ventilation and prone positioning, in ARDS is unrelated to their impact on oxygenation [9, 10]. Similarly, several interventions that improve oxygenation, such as inhaled nitric oxide, are not necessarily associated with improved outcomes [11, 12]. This does not mean that improvements in oxygenation are harmful or not necessary, but rather may not always lie in the causal pathway to improved clinical outcomes.

Dead space

Increased physiological dead space is another marker of ARDS severity, independently correlated with mortality [13]. There are multiple methods for assessing ventilatory efficiency at the bedside [14]. One simple estimation which correlates with dead space is the ventilatory ratio, which adjusts $PaCO_2$ for the degree of minute ventilation [15].

Respiratory mechanics

Respiratory system compliance (and its reciprocal, elastance, $C_{rs} = 1/E_{rs}$) is prognostically important and was embedded in early ARDS severity scores [16]. During the development of the Berlin definition, the addition of compliance did not improve mortality prediction, and it was consequently not included [17]. However, respiratory system compliance is proportional to the size of the aerated lung in ARDS, and therefore inversely proportional to the risk of ventilator-induced lung injury (VILI) through excess stress and strain. Increasingly, we understand that respiratory system compliance is an effect modifier in the response to interventions, and thus plays an important part in tailoring ARDS management [18, 19].

In the assessment of respiratory mechanics, we recommend that all passively ventilated patients with ARDS have regular measurements of total PEEP (PEEPtot; measured during an expiratory hold), plateau pressure (Pplat; measured during an inspiratory hold), static driving pressure (ΔP = Pplat–PEEPtot), and tidal volume (Vt; normalised to predicted body weight by height, PBW). Patients making spontaneous respiratory efforts (assessed visually from ventilator waveforms, or during an expiratory hold manoeuvre or oesophageal manometry) should have the magnitude of their respiratory efforts (and with this, estimates of total lung distending pressure and dynamic lung compliance), and patient–ventilator synchrony assessed.

Take-home message

Acute Respiratory Distress Syndrome (ARDS) can complicate a broad range of medical and surgical conditions and is associated with significant morbidity and mortality. Recent refinements to its definition simplify –and may therefore improve– global recognition. While lung-protective ventilation is now embedded into standard care, other management strategies may require more nuanced application than initially anticipated.

Radiological findings

While bilateral opacities are a hallmark of ARDS, the homogeneity of infiltrates may vary widely, in particular if a focal pathology co-exists or evolves (e.g. community-acquired pneumonia, or aspiration) [20]. Categorising patients by radiological phenotype may assist clinicians in assessing the potential benefit (versus harm) of interventions applied to a non-focal versus focal ARDS morphology.

Molecular biomarkers

Two important biological subphenotypes (Type 1 and 2) have also emerged when molecular biomarkers were considered with clinical variables. Phenotype 2 is less common, accounting for roughly 30% of patients, and has a more inflammatory plasma profile (multiple biomarkers) and a clinical profile consistent with higher heart rate and minute ventilation, lower systolic blood pressure and serum bicarbonate, and greater need for vasopressors [21]. It is associated with a higher mortality and is more common in patients with sepsis-related ARDS and less common in trauma-related ARDS. More recently, simpler models were developed to accurately identify these subphenotypes using only three to four variables (e.g.

interleukin-8, bicarbonate, protein C+/− vasopressor use) [22]. Biological phenotyping is not currently available or recommended outside of clinical trials, but shows potential, as post hoc analyses of several trials have identified benefit (e.g. with a fluid-liberal strategy, or simvastatin administration) in the subgroup of patients with Phenotype 2, even when the overall trials were inconclusive [23, 24].

Right ventricular failure

Right ventricular (RV) dysfunction, failure, and/or acute cor pulmonale is present in approximately 20–25% of patients with ARDS receiving lung-protective ventilation and is an independent risk factor for death [25]. Risk factors include pneumonia as the aetiology of ARDS, $\Delta P \geq 18$ cmH_2O, $PaO_2/FiO_2 < 150$ mmHg, and $PaCO_2 \geq 48$ mmHg [25]. Additional relevant factors to consider may include known or probable pre-morbid RV dysfunction and/or presence of shock.

Close monitoring is recommended in patients with or at risk of RV dysfunction. Echocardiographic trends in RV size and function can be used to serially assess the impact of ventilatory, fluid, and/or RV-focused interventions (e.g. pulmonary vasodilators) [26]. Pulmonary arterial catheterisation facilitates continuous monitoring of pulmonary artery pressures and indices of cardiac output, with some more novel devices offering specific parameters of RV function.

Non-invasive respiratory supports

High-flow nasal oxygen (HFNO)

HFNO offers a method of delivering heated and humidified gas mixtures at much higher flows and FiO_2 than conventional oxygen therapy. Gas flow delivered during expiration may also facilitate dead space washout and increase end-expiratory pressures. The patient interface is generally more comfortable and better tolerated than non-invasive ventilation (NIV) and facilitates communication, expectoration, and oral intake. Until recently, the definition of ARDS necessitated the application of positive pressure. As such, most studies comparing HFNO to conventional oxygen therapy or NIV have been performed in patients with acute hypoxaemic respiratory failure (AHRF), without a specific ARDS label.

Among patients with COVID-19 AHRF and ARDS, HFNO was associated with better clinical outcomes compared to conventional oxygen strategies and is now widely considered the standard of care for patients with AHRF not requiring ventilatory support [27]. Under most circumstances, HFNO may be preferred for patients with mild ARDS (Table 1).

Non-invasive ventilation (NIV)

The use of NIV to manage ARDS is controversial, with broad variation in practice. Positive pressure applied through a helmet or face mask interface can reduce the work of breathing, facilitate alveolar recruitment, and improve oxygenation. NIV can potentially avert the need for invasive mechanical ventilation (IMV) and may reduce mortality [28]. On the other hand, NIV failure is common (incidence ~ 50%) and is associated with a worse prognosis, possibly due to delays in appropriately transitioning patients to IMV [29, 30]. It remains unclear whether NIV failure is a marker of disease severity or whether it may be modifiable by timing of initiation, type of interface, and choice of settings and/or defined thresholds for intubation [31].

In a propensity-matched analysis of the LUNG SAFE study, patients with moderate–severe ARDS ($PaO_2/FiO_2 < 150$ mmHg) receiving NIV had a higher ICU mortality than those receiving IMV [32]. In a single-centre RCT comparing NIV via face mask *versus* helmet in ARDS patients, those in the helmet group had significantly reduced intubation rates, lower mortality, and improved functional outcomes at 1 year [33, 34]. Helmet NIV may be more effective than face mask NIV because of (1) decreased air leak from the interface (hence higher PEEP), which can improve recruitment, ventilation homogeneity, and decrease inspiratory effort, (2) less effective inspiratory assist, potentially limiting VILI, and (3) improved patient comfort and thus less need for analgo-sedation. However, helmet NIV uptake has been limited by the need for a new interface and education.

In patients with mild–moderate ARDS and in the absence of contraindications or other significant organ failures or shock, NIV may be considered, coupled with close monitoring and clearly defined failure criteria. Where available, helmet NIV should be considered, with gradual up-titration of PEEP, targeting a value that minimises the work of breathing, and pressure support to achieve Vt of 6–8 ml/kg PBW. Reliable, non-invasive methods to quantify breathing effort are not yet well validated and/or readily available, and trends in the work of breathing are often inferred from serial clinical examination of extra-diaphragmatic respiratory muscle use. These, together with trends in minute ventilation (and individually Vt; respiratory rate, RR), gas exchange (both oxygenation and acid–base), and consciousness level should be monitored closely to guide assessment of response, need for further titration, and/or declaration of NIV failure. Frequent re-evaluation within the first few hours of initiating therapy, and regularly over the first 24–48 h, is essential, with insufficient improvement across key (patient-specific) variables in a timely fashion prompting appropriate progression to IMV.

Table 1 Summary of key practice recommendations

Non-invasive respiratory support
Non-invasive ventilation
Commence early in patients with mild–moderate ARDS If available, helmet over face mask NIV may be better tolerated Uptitrate PEEP, aiming to optimise the work of breathing Titrate pressure support to target Vt 6–8 ml/kg PBW Monitor closely for changes in tidal volume, minute ventilation, acid–base, work of breathing, hypoxaemia, and haemodynamics Assess success or failure of strategy within 1–2 h of commencement Do not delay intubation when indicated, otherwise continue to review frequently
High-flow oxygen
Commence early in patients with mild ARDS Consider high-flow oxygen preferentially over NIV in patients with high sputum load Target flows 40–60 L/min, as tolerated
Invasive mechanical ventilation
Tidal volume
Target Vt 6 (4–8) ml/kg PBW If $\Delta P \geq 16$ cmH_2O (after PEEP optimisation), consider targeting lower (4–6 ml/kg PBW) range if RR and acid–base allow If known or high risk for RV dysfunction (see below) and acid–base allows (minimise hypercapnoea), target 4–6 ml/kg PBW to reduce mean airway pressure
Plateau pressure
During passive ventilation, target Pplat < 30 cmH_2O If high pleural pressures present (e.g. abdominal distension, central obesity), higher Pplat may be appropriate (e.g. 30–35 cmH_2O); consider use of oesophageal manometry if available If known or high risk for RV dysfunction, following PEEP optimisation, target Pplat < 26–28 cmH_2O, or as low as safely able
Positive end-expiratory pressure
PEEP–FiO_2 table reasonable starting point immediately following intubation, prior to assessment of respiratory mechanics, recruitability, and personalised PEEP titration Lower range of PEEP–FiO_2 table if non-recruitable and concerns for RV or ICP, higher range if anticipating high pleural pressures (e.g. abdominal distension, central obesity) Assess recruitability and benefit of higher PEEP in moderate–severe ARDS Avoid high-PEEP strategy in patients with mild and/or focal ARDS Create and follow local guidelines on PEEP assessment based on local tools and expertise Reassess optimal PEEP regularly, to include change in clinical status and/or following new intervention that may alter respiratory mechanics (e.g. prone position, NMBA)
Controlled mode
Volume or pressure targeted mode as per familiarity of the clinician and unit Consider hybrid mode (e.g. assist control) upfront to aid patient–ventilator synchrony Set appropriate pressure and volume alarms as per targets determined above
Oxygen targets
Target SpO_2 90–95% and/or PaO_2 60–80 mmHg Higher end of target range desirable in patients with acute RV dysfunction
Permissive hypercapnoea
Maintain pH > 7.25 In patients with or at risk of RV dysfunction, tolerance of a permissive hypercapnoea requires serial assessment of haemodynamics and RV function
Non-ventilatory management
Prone positioning
Early (< 36 h from invasive mechanical ventilation and ARDS diagnosis) in patients with $PaO_2/FiO_2 < 150$ mmHg on optimised PEEP and $FiO_2 \geq 0.6$ Daily sessions ≥ 12 h per day, continuing until $PaO_2/FiO_2 \geq 150$ mmHg, PEEP ≤ 10 cmH_2O and $FiO_2 \leq 0.6$ for ≥ 4 h after supination Lack of observable benefit (oxygenation or other) is not an indication to discontinue prone positioning. Discontinue only if safety concerns develop (significant haemodynamic instability, worsening respiratory mechanics, etc.) Neuromuscular blockade is not required by default, but may be appropriate in some cases
Neuromuscular blockade
Consider in early (< 48 h) severe ($PaO_2/FiO_2 \leq 100$ mmHg) ARDS with hypoxaemia Use in moderate–severe ARDS ($PaO_2/FiO_2 \leq 150$ mmHg) with an indication for deep sedation (patient–ventilator dyssynchrony and/or high respiratory drive and effort) Use if impaired respiratory mechanics, after a trial bolus favouring potential benefit Review cessation at 48 h

Table 1 (continued)

Steroids
Use if indicated by other pathology with proven or likely benefit Insufficient evidence to support routine use in ARDS
Fluid management
In patients without shock, a conservative fluid strategy (targeting neutral cumulative fluid balance) initiated early is preferred over diuresis later
Cardiorespiratory monitoring
Ventilation: non-invasive
Clinical assessment of work of breathing and dyspnoea score RR, Vt, minute ventilation, consciousness, heart rate, andblood pressure Oxygenation and acid–base assessment (continuous SpO_2 monitoring and intermittent blood gas analysis) Assess circuit leaks, patient tolerance, and pressure areas
Ventilation: invasive
Passive: PEEPt, Pplat, ΔP (computed from Pplat–PEEPt), Vt (adjusted to PBW), RR Spontaneous efforts; Vt, RR, magnitude of efforts (local institution dependent), patient–ventilator synchrony by ventilator waveform analysis and/or invasive monitoring (e.g. oesophageal manometry) All: continuous pulse oximetry and end-tidal CO_2 monitoring where available, correlate with intermittent blood gas analysis as indicated
Right ventricle
Echocardiographic assessment indicated if (i) pneumonia, (ii) $\Delta P \geq 18$ cmH_2O, (iii) $PaO_2/FiO_2 < 150$ mmHg, (iv) $PaCO_2 \geq 48$ mmHg, (v) shock, and (vi) known or likely pre-existing RV disease Serial echocardiography and/or PAC-based haemodynamic monitoring to guide interventions during IMV if (i) baseline echo is concerning for RV dysfunction, (ii) plan for permissive hypercapnoea, (iii) moderate–severe shock, or (iv) cardiorespiratory deterioration Monitor for shock, renal failure, congestive hepatopathy, and positive fluid balance

ARDS acute respiratory distress syndrome; *Vt* tidal volume; *NIV* non-invasive ventilation; *Pplat* plateau pressure; *PBW* predicted body weight; *ΔP* static driving pressure; *PEEP* positive end-expiratory pressure; *PEEPt* total positive end-expiatory pressure; PaO_2 arterial partial pressure of oxygen; FiO_2 fraction of inspired oxygen; *RR* respiratory rate; *RV* right ventricle; *ICP* intracranial pressure; *PAC* pulmonary artery catheter; *IMV* invasive mechanical ventilation

Ventilator management

The primary goal of IMV is to (i) support adequate gas exchange, (ii) protect the lung from VILI and patient self-inflicted lung injury (PSILI), and (iii) offset the increases in work of the respiratory muscles needed to meet ventilatory demands. At the onset of IMV, when the patient is passive, the focus is on setting the ventilator to provide adequate gas exchange and to optimise lung homogeneity, limiting excess stress and strain.

Low tidal volume ventilation

Lung-protective ventilation strategies have largely been based on the pivotal ARMA trial where Vt 6 (range 4–8) ml/kg PBW, coupled with minimising plateau pressure (Pplat < 30 cmH_2O), reduced mortality in ARDS patients [10]. This strategy has subsequently been shown to benefit a broad spectrum of patients [35], and has become best clinical practice for passively ventilated patients with or without ARDS. Importantly, earlier initiation of a lower Vt strategy yields a greater mortality benefit [36].

The mathematical coupling of Pplat to Vt, mean reducing Vt, offers a simple method of lowering plateau and mean airway pressures without compromising on lung recruitment through lower PEEP. In patients with ARDS and acute cor pulmonale, further limiting plateau pressures to < 26–28 cmH_2O may reduce mortality and offer a strategy for centres where serial echocardiography and/or pulmonary artery catheterisation is not routinely available [37].

Driving pressure and mechanical power

The driving pressure hypothesis posits that the volume of available lung (e.g. baby lung) may vary, and thus Vt should be normalised to respiratory system compliance (Crs), which is a reasonable surrogate for lung volume. Driving pressure (ΔP = Pplat–PEEPt = Vt/Crs) has been shown to mediate the mortality benefit observed across a number of trials comparing Vt and PEEP strategies, suggesting 6 ml/kg PBW may be insufficient to protect against VILI in all patients and in particular among patients with significantly reduced compliance[18, 38]. While large prospective randomised trials (RCTs) are awaited (DRIVE; NCT05440851), the physiological rationale and retrospective data are compelling, and in some expert centres ΔP is being used (target < 16 cmH_2O) to assist with Vt and PEEP selection (Table 2).

In addition to Vt and ΔP, other ventilatory parameters have also been linked to ARDS outcomes. Based on the principle that the energy transferred to the lung during IMV is responsible for VILI, mechanical power (MP; joules per minute) incorporates all of these components into a single variable [39]. In secondary analyses, MP has been shown to independently predict numerous clinical outcomes including mortality; however, computation is complex, with multiple simplified or surrogate equations

Table 2 Common controversies in the medical management of ARDS

	Advantages	Disadvantages	Practice suggestion
High-flow oxygen (vs NIV)	Comfort/tolerance Communication Expectoration Oral intake	Minimal positive airway pressure Minimal additional ventilatory support	Balance clinical benefit with tolerance of NIV Consider impact of sputum volume
Non-invasive ventilation (vs IMV)	Avoids sedation Maintain diaphragm activity Avoid complications of IMV (e.g. infection)	May delay intubation and worsen outcome May not protect against injuriously large patient efforts Risk for aspiration	NIV early in mild–moderate ARDS Take time for titration at bedside Regular review Pre-defined failure (IMV) criteria
High PEEP (vs low PEEP)	Increased alveolar recruitment Protects against atelectotrauma May improve VQ matching and oxygenation	Increased injury by overdistension of the baby lung No consensus on how to identify best PEEP Negative haemodynamic effects	Assess benefit broadly in terms of cardiorespiratory effects (respiratory mechanics, RV, haemodynamics and gas exchange) Avoid in mild ARDS
Driving pressure targeted IMV (vs tidal volume)	Physiologically plausible rationale for benefit Strong retrospective evidence in support	Lacks prospective validation May limit ventilation and worsen acidaemia	Use driving pressure to hone 4–8 ml/kg PBW volume target Consider alongside PEEP
Steroids (vs none)	Indicated for some aetiologies of ARDS (e.g. SARS-CoV-2) Reduces systemic inflammation Possible benefit seen in clinical trials	Potential to induce nosocomial infection, peptic ulceration, and neuromyopathy Inconclusive evidence in clinical trials to date	Give for disease-specific indication Avoid late initiation ($\geq$ 14 d) and/or abrupt discontinuation Await results of ongoing clinical trials
NMBA infusion (vs none)	Reduces oxygen consumption Prevents harm from excessive efforts and dyssynchrony Expiratory muscle relaxation improves lung recruitment	Loss of diaphragm tone; risk atelectasis May increase risk of developing weakness Need for deep sedation; impact on haemodynamics and clinical outcomes	Consider in; Severe ARDS with hypoxaemia Moderate–severe ARDS with large and/or dyssynchronous efforts Need for deep sedation Impaired mechanics responsive to trial bolus
Recruitment manoeuvres (vs none)	Alveolar recruitment when recruitable lung Improvements in VQ matching, oxygenation Improved ventilator homogeneity would protect lung and RV	High-risk for barotrauma Haemodynamic instability common Often requires repeating (due to loss of high PEEP)	Prolonged RM have shown harm No evidence of benefit from shorter RM No role for any RM in current routine practice
Early spontaneous breathing in IMV (vs passive)	Beneficial effects of maintaining safe levels of diaphragm activity on lung and diaphragm In select patients may shorten IMV duration	Injuriously large and/or dyssynchronous efforts common Difficult to control with sedation and ventilation alone	Consider in mild–moderate ARDS, if acceptable respiratory mechanics Couple with close monitoring of respiratory effort
Pulmonary artery catheter (vs none)	Continuous invasive haemodynamic parameters to monitor and guide intervention Requires less training than echocardiography Less operator dependent than echocardiography	Serially performed echocardiography yields equivalent information non-invasively Invasive procedure Requires training to insert, manage and interpret	Consider if serial echocardiography not available and signs of RV failure or acute cor pulmonale on screening echocardiography Ensure adequacy of staff training if used

NIV non-invasive ventilation; *IMV* invasive mechanical ventilation; *ARDS* acute respiratory distress syndrome; *VQ* ventilation/perfusion; *PEEP* positive end-expiratory pressure; *NMBA* neuromuscular blocking agent; *RM* recruitment manoeuvre; *RV* right ventricle

proposed. One large retrospective analysis of six lung-protective ARDS trials found that a simpler model incorporating ΔP and RR alone provided a potentially superior predictor of mortality than MP [40]. Importantly, ΔP was found to be four times more influential than RR, and while prospective trials are required, this finding further supports the importance of ΔP, while highlighting the potential impact of RR. In ARDS patients requiring a higher target minute ventilation to achieve pH and $PaCO_2$ targets, this simple concept (targeting the lowest computed value of '$4\times\Delta P + RR$' for a given minute ventilation) may help to balance the trade-off of up-titrating RR versus small increments in Vt.

Recruitability

Recruitment refers to the potential of collapsed or partially collapsed alveolar units to reopen with the application of higher airway pressures, thereby increasing overall lung volume and decreasing the risk of excess stress with applied pressure. In highly recruitable lungs, higher PEEP can reopen collapsed alveoli, improve oxygenation, reduce cyclic atelectrauma, and prevent VILI. In non-recruitable lungs, increased PEEP may primarily overdistend already open alveoli, increasing the risk of barotrauma and haemodynamic compromise without improving gas exchange. Therefore, tailoring PEEP based on recruitability may maximise benefit and minimise harm.

Several techniques are used to assess lung recruitability in ARDS. Thoracic CT scanning, the research gold standard, quantifies the amount of non-aerated lung that can be recruited at higher pressures, but its clinical utility is limited by radiation exposure, transport logistics, cost, and time [41]. Static or low-flow pressure–volume curves can also provide insight, where a lower inflection point suggests a threshold for airway opening, after which alveolar recruitment may occur [42, 43].

A more accessible method is to evaluate oxygenation response to stepwise increases (or decreases) in PEEP; an improvement in oxygenation may indicate recruitment, but can be confounded by changes in perfusion or haemodynamics (e.g. decreased cardiac output in the context of high shunt fraction may paradoxically increase oxygenation). While ultrasound is a useful tool to detect subpleural de-aeration and re-aeration, it has limited capacity to differentiate recruitment from overdistension [44, 45]. Training and time to undertake the comprehensive evaluation needed for structured scoring may further limit the uptake of this technique [45, 46].

Electrical impedance tomography (EIT) offers dynamic imaging of regional ventilation and shows promise in identifying recruitment and overdistention [47], but availability is limited. Current approaches using EIT rely on the assumption that alveolar overdistension and collapse are equally injurious, with optimal PEEP described as the best trade-off between the two; while animal data support this hypothesis, clinical data are pending [48].

The recruitment-to-inflation (R/I) ratio is a simple bedside measure that expresses the compliance of the lung volume recruited by high PEEP, relative to the compliance of the lung measured at low PEEP. Recruited lung volume is calculated as the difference between the actual and predicted expiratory volume—the latter derived from compliance at low PEEP—following a one-breath PEEP reduction of at least 10 cmH_2O [49]. For reliable assessment of respiratory mechanics, the low PEEP level must remain above airway opening pressure (pressure at which volume starts to increase during a low flow inflation breath). An R/I ratio above 0.5 suggests greater recruitability, whereas lower values reflect a higher risk of overdistension.

Positive end-expiratory pressure (PEEP)

Choosing the right PEEP has been the subject of clinical investigation for over 50 years [50]; however, the optimal PEEP level remains controversial, especially in moderate-to-severe ARDS, where both high and low PEEP strategies have potential advantages and potential risks.

PEEP strategies tested have been guided by lung-protective concepts (limiting Pplat) [51], respiratory mechanics (pressure–volume loops, static compliance, stress index, end-expiratory transpulmonary pressure) [42, 43, 49, 52–54], gas exchange [55], or bedside imaging (EIT, lung ultrasound) [47, 56] assessment (Table 3), with some of these trials also incorporating recruitment manoeuvres.

Non-focal ARDS is more likely to exhibit recruitability, and higher PEEP may open collapsed alveoli and reduce VILI. In contrast, focal ARDS is often non-recruitable, and higher PEEP may cause overdistention of healthy lung units and worsen injury. This concept was explored in the LIVE study (2019), which tested a personalised ventilation strategy based on lung morphology alone, without assessment of recruitment response per se [57]. The study found no overall benefit, but furthermore showed that misclassification was associated with increased harm, reinforcing the need for—and present difficulty with—accurate prospective phenotyping.

Several large RCTs have evaluated higher vs lower PEEP strategies: the ALVEOLI (2004), LOVS (2008), and Express (2008) trials compared higher vs lower PEEP in the context of low Vt ventilation [51, 58, 59]. Individually, none showed a mortality benefit with higher PEEP. However, a pooled analysis of these three trials showed that higher PEEP reduced mortality in patients with moderate-to-severe ARDS ($PaO_2/FiO_2 < 200$ mmHg), but not in patients with mild ARDS, suggesting a potential benefit in more severe disease [60]. The ART trial (2017) tested a high-PEEP strategy with aggressive lung recruitment manoeuvres and found higher mortality and more barotrauma in the intervention group, raising concerns about overly aggressive PEEP titration and prolonged recruitment manoeuvres [54].

Oesophageal manometry to target a positive end-expiratory transpulmonary pressure (TPP = airway pressure–oesophageal pressure) is a physiologically attractive method of titrating PEEP to prevent atelectasis. Early studies found an association with improvements in oxygenation and compliance [61]; however, a subsequent

Table 3 Advantages and disadvantages of PEEP titration methods

	Method description	Advantage	Disadvantage
Oxygenation			
PEEP–FiO_2 table	Reference table; FiO_2 requirement determines PEEP target range	Simple Widely available	Oversimplistic FiO_2 choice not standardised Range rather than best PEEP
Oxygenation response	Oxygenation response to; (i) change in PEEP (e.g. lower vs higher), or (ii) as part of a decremental PEEP trial	Simple Widely available Focus on optimising hypoxaemia	Oxygenation is a poor surrogate for recruitment Reduction in cardiac output may mean disconnect with oxygen delivery
Respiratory mechanics			
Pressure–volume loop	PEEP set 2 cmH_2O above inspiratory lower inflection point of PV loop (quasi-static ventilator measurement at low flow)	Automated on many ventilators Low flow inflation can also be performed manually on most other ventilators	May underestimate PEEP due to conditions of low flow Subjectivity in determining inflection point May miss AOP
Driving pressure (elastance or compliance)	PEEP that yields lowest driving pressure (at a fixed Vt) or, best compliance or elastance (fixed Vt or driving pressure)	Measurable on most ventilators Simple to perform Solid physiological basis Does not need specific starting PEEP	Does not differentiate tidal from sustained recruitment Requires patient to be passively ventilated May miss regional overdistension
Stress index	Pressure–time curve assessed during constant (square) inspiratory flow; concave (tidal recruitment/collapse), linear (ideal), convex (overdistension)	Available to perform on most ventilators In volume-targeted mode (with square flow waveform), continuous visualisation possible	Quantification usually requires specialised equipment Visual assessment subjective Does not account for regional variations
Oesophageal manometry	PEEP that yields an end-expiratory transpulmonary pressure of around zero	Accounts for pleural pressure in assessment of lung distending pressure Solid physiological basis	Semi-invasive technique Requires equipment, training and re-calibration Global measures only
Imaging			
Computerised tomography	Volume of lung collapsed vs overdistended assessed at multiple PEEP levels	Gold standard measure of recruitable lung volume Assesses overdistension Regional assessment	Transport safety concerns Impact of supine position on measures is unknown Not readily repeatable Radiation exposure risks
Electrical impedance tomography	Decremental PEEP manoeuvre allows assessment of collapse and overdistension; crossing point determines optimal PEEP	Available at the bedside Non-invasive Repeatable Regional assessment Considers both collapse and overdistension	Requires equipment and training Unclear if crossing point is optimal trade-off Contraindications exist (e.g. implanted electrical devices)
Lung ultrasound	Systematic assessment of lung regions for de-aeration and re-aeration in response to changes in PEEP	Available at the bedside Non-invasive Repeatable Able to identify other pathologies e.g. effusion	Requires training Limited ability to differentiate recruitment from overdistension Comprehensive examination needed, with application of a structured scoring system
Haemodynamics			
Echo-cardiography	Serial assessment of RV size, function and pulmonary artery pressures during PEEP titration	Available at the bedside Non-invasive Repeatable RV metrics may reflect beneficial recruitment	Comprehensive training needed Time consuming Not a direct assessment of VILI risk

PEEP positive end-expiratory pressure; *FiO_2* fraction of inspired oxygen; *Vt* tidal volume, *RCT* randomised controlled trial; *PV* pressure–volume; *AOP* airway opening pressure; *RV* right ventricle; *VILI* ventilator-induced lung injury

large RCT failed to show a clinical benefit when used in all-comers with moderate–severe ARDS and when compared with use of the higher PEEP–FiO_2 table [53]. A subsequent post hoc analysis of this trial, however, found a strong interaction with APACHE2, with a sustained mortality benefit (at 1 year) favouring an oesophageal-guided PEEP strategy in patients with a low APACHE2 score, while the empirical high-PEEP strategy was favoured in those with a high baseline APACHE2 score [62]. Furthermore, mortality was found to be lowest when end-expiratory TPP was 0 (± 2) cmH_2O regardless of treatment group assignment.

PEEP–FiO_2 tables offer a pragmatic approach to setting PEEP, since they are easy to implement. The tables may be of value immediately upon initiation of invasive mechanical ventilation, prior to detailed cardiorespiratory assessment and personalised PEEP selection. While low-to-moderate PEEP remains the standard, especially in patients with mild ARDS, moderate-to-high PEEP may benefit carefully selected patients with moderate-to-severe ARDS, particularly if they have recruitable lung units. Importantly, the evidence discourages a one-size-fits-all approach, and improvements in PaO_2/FiO_2 or reduction in FiO_2 requirements alone should not be interpreted as reliable markers of best PEEP. Personalised strategies based on lung mechanics, morphology, RV size and performance, or biological subphenotypes may optimise PEEP titration, but further research is needed to operationalise. In the interim, approaches need to be tailored to locally available equipment and expertise e.g. Fig. 1.

Fraction of inspired oxygen

Dependency on supplemental oxygen to prevent hypoxaemia is embedded into the ARDS diagnostic criteria. Setting an appropriate FiO_2 is important because hyperoxia and hypoxia are independently associated with mortality in ARDS [63], and because FiO_2 impacts severity

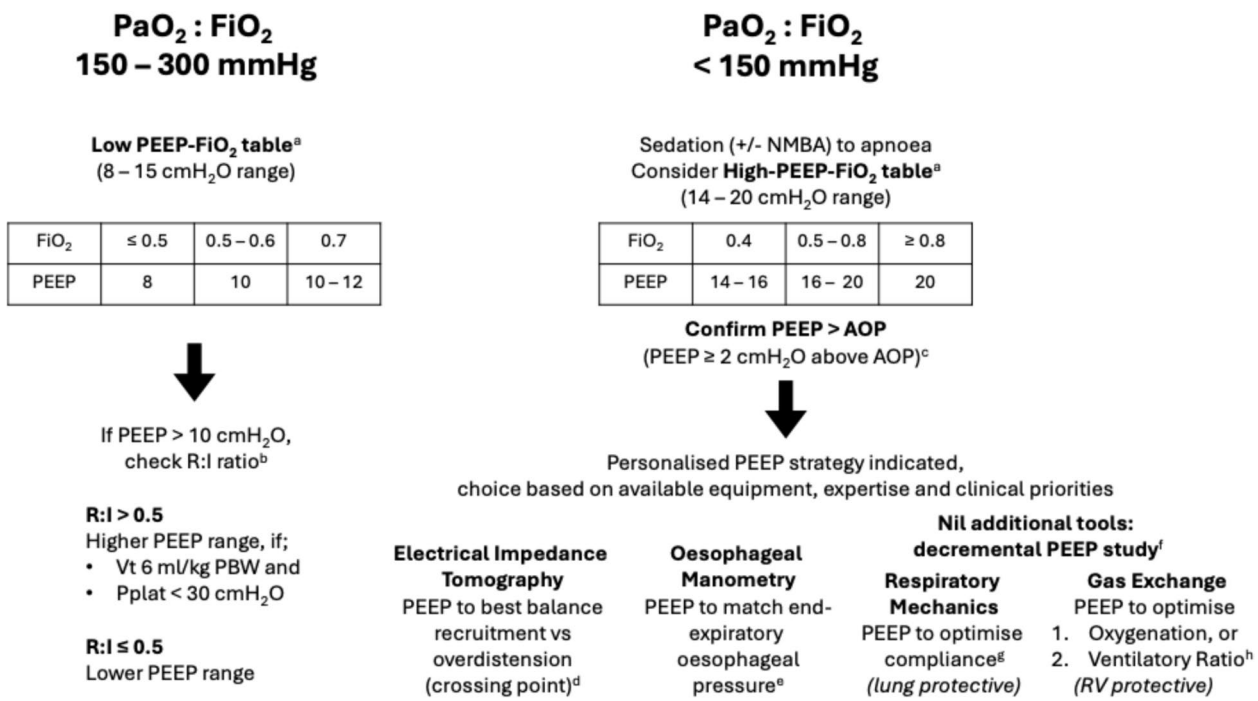

Fig. 1 A practical guide to optimising PEEP during invasive mechanical ventilation in ARDS. [a]Low and high PEEP -FiO_2 tables from the 2004 ARDSnet PEEP trial [58]. High PEEP in moderate–severe ARDS may be particularly beneficial if hyperinflammatory phenotype and/or non-focal ARDS. [b]Recruitment-to-inflation ratio to be performed as previously described [49]. [c]Consider measuring airway opening pressure (AOP) by means of a slow inflation manoeuvre starting at or slightly below current PEEP level. If AOP above PEEP, consider increasing PEEP to 0–2 cm H_2O above measured AOP. [d]Optimal PEEP selected using electrical impedance tomography to balance recruitment and overdistension [47]. [e]Equivalent to targeting a transpulmonary pressure at end expiration of 0 (± 2) cmH_2O [53]. [f]Start at highest acceptable PEEP (e.g. based on Pplat target) if haemodynamics tolerate [51]. [g]Optimal PEEP selected on that which yields lowest static driving pressure (volume-targeted mode) or highest static compliance (volume or pressure-targeted mode) as previously described [38]. [h]Optimal PEEP selected based on that which optimises ventilatory ratio, computed as previously described [15]. *PaO_2* arterial partial pressure of oxygen; *FiO_2* fraction of inspired oxygen; *PEEP* positive end-expiratory pressure; *R:I* recruitment-to-inflation ratio; *Vt* tidal volume; *PBW* predicted body weight; *Pplat* plateau pressure; *NMBA* neuromuscular blocking agent; *AOP* airway opening pressure; *RV* right ventricular

classification and thus eligibility for specific interventions. A liberal oxygen strategy has been shown to be harmful in critically ill patients, yet trials with a conservative arm that allows permissive hypoxaemia have similarly shown harm [64, 65]. In the HOT-ICU trial, patients with AHRF were randomised to receive a PaO_2 target of 60 mmHg versus 90 mmHg, with no difference in 90-day mortality (primary outcome) or any secondary outcomes [66]. Until further evidence comes to light, targeting a PaO_2 60–80 mmHg (or SpO_2 90–95%) is appropriate, adjusting for relevant disease or patient-specific conditions.

Permissive hypercapnoea

Reductions in Vt, ΔP, and/or RR often necessitate a strategy of permissive hypercapnoea [67]. The degree of acceptability of hypercapnoea should be judged in conjunction with the patient's acid–base status (targeting pH > 7.25), with appropriate efforts to correct significant metabolic contributors to acidaemia. While tolerating moderate levels of hypercapnoea can allow greater lung protection, high $PaCO_2$ (e.g. ≥ 50 mmHg) has been independently associated with mortality in moderate–severe ARDS [68] however, residual confounding by severity may remain. Nonetheless, particular attention should be taken to patients with haemodynamic instability, known RV dysfunction, or elevated intracranial pressure who are less tolerant of acute hypercapnoea irrespective of the presence or absence of acidaemia. All patients undergoing a strategy of permissive hypercapnoea should have serial monitoring of acid–base, haemodynamics, and RV function to map tolerance and trends. The role of extracorporeal devices is covered in a separate review [69].

Non-ventilatory management

Prone positioning

Prone positioning produces a more homogenous delivery of ventilation, facilitating recruitment of well-perfused collapsed dorsal lung regions, while stabilising the anterior chest wall, decreasing chest wall compliance and protecting against overdistension of ventral lung regions. Corresponding reductions in pulmonary vascular resistance offload the RV and confer protection. The PROSEVA trial used 12–24 h (mean = 17 h) and early intervention (< 36 h of IMV) in patients with moderate–severe ARDS (PaO_2/FiO_2 < 150 mmHg, PEEP ≥ 5 cmH_2O and FiO_2 ≥ 0.6) [9]. Mortality at 28 days was halved in the intervention group. A network meta-analysis of various protective ventilation strategies for moderate–severe ARDS found that a combination of low Vt and prone positioning yielded the greatest mortality benefit [70]. Prone position is now a standard of care practice for moderate-to-severe ARDS patients.

Absolute contraindications to prone positioning are limited to patients with unstable spinal or pelvic injuries or open chest/abdomen. With appropriate monitoring (e.g. intracranial pressure monitoring in brain-injured patients), the benefit–harm risk amongst those with relative contraindications may be individualised. Importantly, mortality benefit has not been shown to be related to oxygenation response, and patients should continue to receive prone ventilation until no longer indicated (PaO_2/FiO_2 ≥ 150 mmHg, PEEP ≤ 10 cmH_2O and FiO_2 ≤ 0.6, for ≥ 4 h after supination) or the development of clinically important contraindications.

Neuromuscular blockade

Neuromuscular blocking agents (NMBA) have theoretical advantages in ARDS patients by mitigating excess lung stress and strain generated by large and/or dyssynchronous inspiratory efforts [71]. Secondly, expiratory muscle relaxation can protect against de-recruitment and has been shown to increase end-expiratory lung volume and improve oxygenation [72, 73]. Finally, increases in respiratory muscle oxygen consumption due to increased mechanical work may be ablated by NMBA [74]. In a secondary analysis of the ROSE trial, the beneficial effects of NMBA varied according to baseline respiratory system elastance, supporting the hypothesis that patients with high elastance and at higher risk of VILI and PSILI may have a much higher probability of benefiting from early neuromuscular blockade [19].

NMBA administration is not a panacea; however, the postulated benefits need to be carefully balanced against potential harms. Firstly, loss of diaphragmatic tone is associated with cephalad displacement of the diaphragm, which can worsen atelectasis and collapse of the dependent lung regions [75]. Secondly, deep sedation—a necessary concomitant sedation strategy—has been independently linked to worse clinical outcomes in critically ill patients; furthermore, it may exacerbate haemodynamic instability in this high-risk cohort [76]. Partial neuromuscular blockade may balance some of the putative benefits against these harms in specific subgroups, but this requires confirmation in prospective clinical trials [77].

The ACURASYS and ROSE trials produced divergent results largely due to differences in study design, clinical practices, and evolving standards of care. ACURASYS suggested that early, short-term use of NMBA could improve survival in patients with moderate-to-severe ARDS, likely due to better control of patient–ventilator synchrony and reduced lung injury in a context where deep sedation was routine [78]. However, by the time of

the ROSE trial, nearly a decade later, ICU management had evolved to lighter sedation, higher PEEP strategies, and other lung-protective measures. These improvements likely improved outcomes in the control group, possibly diminishing any additional benefit from NMBA. These changes in standard of care may explain why ROSE did not demonstrate a mortality benefit and highlighted the potential risks of routine deep sedation and paralysis, such as ICU-acquired weakness [79]. The findings suggest that neuromuscular blockade should not be used routinely in all ARDS patients, but may still play a role in select cases—such as patients with profound hypoxaemia, severe dyssynchrony, or when lung-protective ventilation is otherwise not achievable.

Steroids

Corticosteroids have an established indication across a number of specific diseases associated with ARDS (e.g. COVID-19, *Pneumocystis jirovecii* in patients with HIV, or organising pneumonia), with a possible benefit among other overlapping patient cohorts (e.g. septic shock, and/or severe community-acquired pneumonia) [80]. In patients without an established indication or contraindication, their role remains controversial. Early short durations have not been shown to be beneficial, with late initiation of steroids associated with potential harm [81, 82]. One patient-data and trial-level meta-analysis of four RCTs found that prolonged ($\geq$7 days) low-dose methylprednisolone (1 mg/kg/d), initiated early (<72 h) with a tapering dose, reduced the duration of mechanical ventilation and hospital mortality [83]. Importantly in that analysis, prolonged glucocorticoid treatment was not associated with an increased risk of developing nosocomial infections, and in another study it was not independently associated with the development of neuromyopathy [84].

Most recently, the DEXA-ARDS trial randomised patients with recent onset (<30 h) moderate–severe ARDS ($PaO_2/FiO_2 \leq 200$ mmHg under standardised ventilator settings after 24 h of screening) to standard care with or without unblinded co-administration of dexamethasone (20 mg day 1–5, 10 mg day 6–10 or extubation) [85]. Despite stopping early for slow enrolment (88% planned recruitment), the trial found an improvement in ventilator-free days and 60-day mortality with dexamethasone, with associated increased rates of hyperglycaemia. While some clinicians may interpret these data as evidence that early low–moderate dose glucocorticoids weaned slowly are beneficial in IMV patients with moderate–severe ARDS, many consider the evidence as inconclusive. Two ongoing prospective clinical trials (GuARDS; ISRCTN15076735 and CORT-E2; NCT05440851) aim to elucidate this further.

Fluid management and diuresis

A high cumulative fluid balance is associated with increased mortality among patients with ARDS, as with multiple other critically ill cohorts [86]. In ARDS, excess fluid may worsen pulmonary oedema and RV dysfunction, worsening gas exchange, lung mechanics, and contribute to multiorgan venous congestion. In the FACCT trial, although the conservative fluid strategy did not confer a statistically significant reduction in 60-day mortality (25.5% vs 28.4% in conservative vs liberal groups respectively, $p = 0.30$), it was associated with improvements in oxygenation and lung injury scores, more ventilator-free days, and shorter ICU lengths of stay [87]. A restrictive fluid strategy should be considered once shock has resolved in patients with ARDS, in particular in the presence of moderate–severe impairment in oxygenation or RV dysfunction.

Summary

Early recognition of ARDS prioritises identification and treatment of any underlying pathology and refocuses supportive care to protect the lung and other organs from injury. ARDS severity can be assessed from a number of indices of cardiorespiratory performance, each of which may refine selection or delivery of beneficial interventions for individual patients.

Non-invasive respiratory support plays a role in early mild ARDS for many, but requires close monitoring strategies and clear criteria for failure to avoid delays in intubation. IMV with low Vt and an individualised PEEP assessment forms core ARDS ventilator management. Clinicians and units should develop guidelines for PEEP titration based on locally available equipment and training, and methods for ensuring and auditing safe Vt practices. Close observation for excessive and/or dyssynchronous respiratory efforts necessitates embedding the monitoring of these into routine practice. Potential benefit from NMBA and steroids requires individualised assessment, whereas thresholds for initiating prone positioning should be protocolised.

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Declarations

Conflicts of interest

ISM declares no conflicts of interest. MA declares grants from Timpel S.A., Covidien/Medtronic, Orange Med/Nihon Koden, and Madnamed Lung Ventilators, alongside consulting fees from Timpel S.A. and Magnamed Lung Ventilators, personal fees from Medtronics, and shares in Timpel S.A. EBK has received lecturing fees from Hamilton Medical Inc. outside the submitted work and has received a KL2 award from Harvard Catalyst, The Sciences, National Institutes of Health award No. TR002542. GB reports consulting fees from Flowmeter SPA and Gaea OU, personal fees from Draeger Medical and Fisher and Paykel, alongside stock in DICO technologies. CSC receives research support from the National Institutes of Health and the US Department of Defense (to her institution); her institution previously received support for her research from Roche–Genentech. She has served as a consultant to Arrowhead, Calcimedica, EnliTISA, Novartis, Aerogen, Boehringer Ingelheim, Merck, Healios, Matisse, Vasomune, and Gen1e Life Sciences. LH receives consultancy fees from Liberate Medical (USA), and research grants from Pulmotech (the Netherlands) and Liberate Medical (USA). CLH receives funding from an NHMRC Investigator Grant (GNT2033103). PN declares no conflicts of interest. ASN declares no conflicts of interest. SS receives funding from the NIH/NHLBI, DoD/USAMRAA, alongside personal consulting fees from Getinge Inc. CS is Chair of the UKRI-Medical Research Council Experimental Medicine Panel, and her institution receives funding to support her research from UKRI-Medical Research Council (MR/X005070/1; MR/S035753/1), the National Institute for Health and Care Research (NIHR133788), and the Wellcome Trust. IT receives funding from CIHR, alongside teaching honoraria from Getinge Inc., and her personal partner holds equity in MbMED S.A. TY declares no conflicts of interest. AS has received funding from Vantive, Predicate, Signal-1, safeBVM, and Thornhill Medical. NDF has received consulting fees from Baxter Inc. Carol Hodgson is a Section Editor for Intensive Care Medicine. She has not taken part in the review or selection process of this article.

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